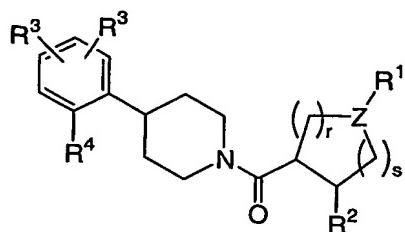


WHAT IS CLAIMED IS:

1. A compound of structural formula I:



(I)

5

or a pharmaceutically acceptable salt thereof;

wherein:

R¹ is selected from the group consisting of:

- 10 (1) hydrogen,
 (2) amidino,
 (3) C₁₋₄ alkyliminoyl,
 (4) C₁₋₁₀ alkyl,
 (5) -(CH₂)_n-NR⁷R⁸,
 15 (6) -(CH₂)_n-C₃₋₇ cycloalkyl,
 (7) -(CH₂)_n-phenyl,
 (8) -(CH₂)_n-naphthyl, and
 (9) -(CH₂)_n-heteroaryl,

20 wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

R² is selected from the group consisting of:

- 25 (1) phenyl,
 (2) naphthyl, and
 (3) heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³;

- 30 each R³ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,
- 5 (5) -(CH₂)_n-heteroaryl,
- (6) -(CH₂)_n-heterocycloalkyl,
- (7) -(CH₂)_nC₃₋₇ cycloalkyl,
- (8) halogen,
- (9) OR⁶,
- 10 (10) -(CH₂)_nN(R⁶)₂,
- (11) -(CH₂)_nC≡N,
- (12) -(CH₂)_nCO₂R⁶,
- (13) NO₂,
- (14) -(CH₂)_nNR⁶SO₂R⁶,
- 15 (15) -(CH₂)_nSO₂N(R⁶)₂,
- (16) -(CH₂)_nS(O)_pR⁶,
- (17) -(CH₂)_nNR⁶C(O)N(R⁶)₂,
- (18) -(CH₂)_nC(O)N(R⁶)₂,
- (19) -(CH₂)_nNR⁶C(O)R⁶,
- 20 (20) -(CH₂)_nNR⁶CO₂R⁶,
- (21) -(CH₂)_nNR⁶C(O)-heteroaryl,
- (22) -(CH₂)_nC(O)NR⁶N(R⁶)₂,
- (23) -(CH₂)_nC(O)NR⁶NR⁶C(O)R⁶,
- (24) O(CH₂)_nC(O)N(R⁶)₂,
- 25 (25) CF₃,
- (26) CH₂CF₃,
- (27) OCF₃, and
- (28) OCH₂CF₃,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, and wherein any methylene (CH₂) carbon atom in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

35

R⁴ is selected from the group consisting of:

- (1) $-(CH_2)_n-N(R^5)-NR^5R^6$,
- (2) $-(CH_2)_n-N(R^5)-(CH_2)_q-NR^5R^6$,
- (3) $-(CH_2)_n-N(R^5)-C(=NR^5)-NR^5R^6$,
- (4) $-(CH_2)_n-N(R^5)-(CH_2)_q-N(R^5)-(C=NR^5)-NR^5R^6$,
- 5 (5) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(N(R^5)_2)-(CH_2)_q-OR^6$,
- (6) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_n-R^6$,
- (7) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-S(O)p-R^6$,
- (8) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-NR^5R^6$,
- 10 (9) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_n-R^6$,
- (10) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-S(O)p-R^6$,
- (11) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-NR^5R^6$,
- (12) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(N(R^5)_2)(CH_2)_q-O-R^6$, and
- (13) $-(CH_2)_n-N(R^5)-R^9$,

wherein $(CH_2)_n$ is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁵ is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl, and
- 20 (3) C(O)C₁₋₆ alkyl,

wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁶ is selected from the group consisting of:

- 25 (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) C(O)C₁₋₆ alkyl,
- (4) $-(CH_2)_nC_{3-7}$ cycloalkyl,
- (5) $-(CH_2)_nC_{2-7}$ heterocycloalkyl,
- 30 (6) $-(CH_2)_n$ -phenyl,
- (7) $-(CH_2)_n$ -naphthyl,
- (8) $-(CH_2)_n$ -heteroaryl, and
- (9) $-(CH_2)_nC_{3-7}$ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl,

hydroxy, and C₁₋₄ alkoxy, or wherein two R⁶ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

5 each R⁷ and R⁸ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) amidino,
- (3) C₁₋₄ alkyliminoyl,
- (4) C₁₋₁₀ alkyl,
- 10 (5) -(CH₂)_n-C₃₋₇ cycloalkyl,
- (6) -(CH₂)_n-phenyl,
- (7) -(CH₂)_n-naphthyl, and
- (8) -(CH₂)_n-heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups

15 independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

R⁹ is selected from the group consisting of:

- (1) alanine,
- (2) glycine,
- (3) proline,
- (4) cysteine,
- (5) histidine,
- (6) glutamine,
- 25 (7) aspartic acid,
- (8) isoleucine,
- (9) arginine,
- (10) glutamic acid,
- (11) lysine,
- (12) serine,
- 30 (13) phenylalanine,
- (14) leucine,
- (15) threonine,
- (16) tryptophan,
- 35 (17) methionine,

- (18) valine,
(19) tyrosine,
(20) asparagine,
(21) 2-amino adipic acid,
5 (22) beta-alanine,
(23) 2-aminoheptanedioic acid,
(24) 2-aminobutyric acid,
(25) 4-aminobutyric acid,
(26) 2,4-diaminobutyric acid,
10 (27) citrulline,
(28) cycloserine,
(29) norvaline,
(30) norleucine,
(31) ornithine,
15 (32) penicillamine,
(33) phenylglycine,
(34) phenylisoserine,
(35) phenylstatine,
(36) pipecolic acid,
20 (37) piperidine carboxylic acid,
(38) pyroglutamic acid,
(39) sarcosine,
(40) statine,
(41) allo-threonine,
25 (42) t-leucine,
(43) 2-aminoisobutyric acid, and
(44) 3-aminoisobutyric acid;

Z is selected from the group consisting of:

- 30 (1) C(R¹), and
(2) N;

r is 1 or 2;

s is 0, 1, or 2;

35 n is 0, 1, 2, or 3;

p is 0, 1, or 2; and

q is 1, 2, 3, or 4.

2. The compound of Claim 1 wherein R¹ is selected from the group consisting of: hydrogen, C₁₋₆ alkyl, -(CH₂)₀₋₁C₃₋₆ cycloalkyl, and

5 -(CH₂)₀₋₁-phenyl, wherein phenyl is unsubstituted or substituted with one to three groups independently selected from R³, and alkyl and cycloalkyl are optionally substituted with one to three groups independently selected from R³ and oxo; and pharmaceutically acceptable salts thereof.

10 3. The compound of Claim 2 wherein R² is phenyl or thieryl, optionally substituted with one to three groups independently selected from R³; and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 wherein R² is phenyl optionally substituted with one to three groups independently selected from R³; and pharmaceutically acceptable salts thereof.

15 5. The compound of Claim 1 wherein each R³ is independently selected from the group consisting of: C₁₋₆ alkyl, -(CH₂)_n-phenyl, -(CH₂)_n-heteroaryl, -(CH₂)_nC₂₋₇ heterocycloalkyl, -(CH₂)_nC₃₋₇ cycloalkyl, halogen, OR⁵, -(CH₂)_nN(R⁵)₂, -(CH₂)_nCO₂R⁵, NO₂, and CF₃, wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, and wherein alkyl, cycloalkyl, heterocycloalkyl, and (CH₂)_n are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group; and pharmaceutically acceptable salts thereof.

25

6. The compound of Claim 1 wherein R⁴ is selected from the group consisting of:

(1) -(CH₂)_n-N(R⁵)-NH₂,

(2) -(CH₂)_n-N(R⁵)-(CH₂)_q-NH₂,

(3) -(CH₂)_n-N(R⁵)-(CH₂)_n-NR⁵R⁶,

30 (4) -(CH₂)_n-N(R⁵)-(CH₂)_n-NHC₁₋₆ alkyl,

(5) -(CH₂)_n-N(R⁵)-(CH₂)_n-N(C₁₋₆ alkyl)₂,

(6) -(CH₂)_n-N(R⁵)-(CH₂)_n-NHC(O)C₁₋₆ alkyl,

(7) -(CH₂)_n-N(R⁵)-(CH₂)_n-N(R⁵)C(O)C₁₋₆ alkyl,

(8) -(CH₂)_n-N(R⁵)-(CH₂)_n-N(C(O)C₁₋₆ alkyl)₂,

35 (9) -(CH₂)_n-N(R⁵)-C(=NH)-NH₂,

(10) -(CH₂)_n-N(R⁵)-(CH₂)_q-NH(C=NH)-NH₂,

- (11) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-OH$,
(12) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-OC_{1-6}$ alkyl,
(13) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-OR^6$,
5 (14) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_n$ -heteroaryl,
(15) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_n-R^6$,
(16) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-SH$,
(17) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-S-C_{1-6}$ alkyl,
10 (18) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-S-R^6$,
(19) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-NH_2$,
(20) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-NHR^6$,
(21) $-(CH_2)_n-N(R^5)-(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-NR^5R^6$,
15 (22) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(NH_2)(CH_2)_n$ -heteroaryl,
(23) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-SH$,
(24) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-S-C_{1-6}$ alkyl,
15 (25) $-(CH_2)_n-N(R^5)-C(O)(CH_2)_n-C(R^5)(NH_2)(CH_2)_q-NR^5R^6$, and
(26) $-(CH_2)_n-N(R^5)-R^9$,

wherein alkyl and $(CH_2)_n$ are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy, and heteroaryl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy; and pharmaceutically acceptable salts thereof.

20 7. The compound of Claim 1 wherein R⁶ is selected from the group consisting of: hydrogen, C₁₋₆ alkyl, C(O)C₁₋₆ alkyl, and $-(CH_2)_n$ -heteroaryl; and pharmaceutically acceptable salts thereof.

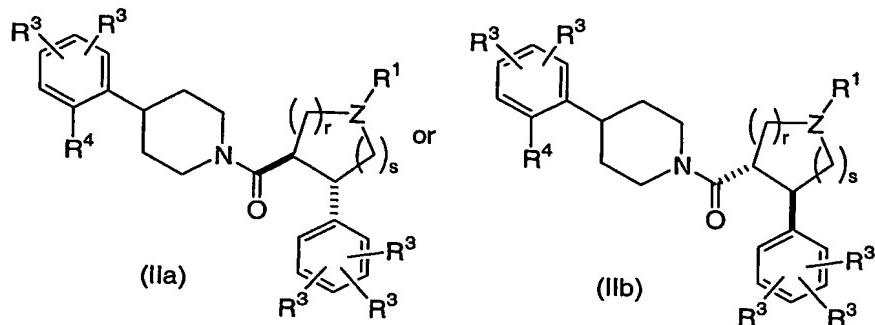
25 8. The compound of Claim 5 wherein Z is CR¹; and pharmaceutically acceptable salts thereof.

30 9. The compound of Claim 6 wherein Z is N; and pharmaceutically acceptable salts thereof.

10. The compound of Claim 1 wherein r is 1 and s is 1; and pharmaceutically acceptable salts thereof.

35 11. The compound of Claim 1 wherein r is 2 and s is 1; and pharmaceutically acceptable salts thereof.

12. The compound of Claim 1 of structural formula IIa or IIb of the indicated *trans* relative stereochemical configuration:



- 5 or a pharmaceutically acceptable salt thereof;
wherein:

R^1 is selected from the group consisting of: hydrogen, amidino, C₁₋₄ alkyliminoyl, C₁₋₆ alkyl, C₅₋₆ cycloalkyl, -(CH₂)₀₋₁ phenyl, and -(CH₂)₀₋₁ heteroaryl, wherein phenyl and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R^3 , and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R^3 and oxo:

each R³ is independently selected from the group consisting of:

- (1) hydrogen,
 - (2) C₁-6 alkyl,
 - (3) -(CH₂)_n-phenyl,
 - (4) -(CH₂)_n-naphthyl,
 - (5) -(CH₂)_n-heteroaryl,
 - (6) -(CH₂)_n-heterocycloalkyl,
 - (7) -(CH₂)_nC₃-7 cycloalkyl,
 - (8) halogen,
 - (9) OR⁶,
 - (10) -(CH₂)_nN(R⁶)₂,
 - (11) -(CH₂)_nC≡N,
 - (12) -(CH₂)_nCO₂R⁶,
 - (13) NO₂,
 - (14) -(CH₂)_nNR⁴SO₂R⁶,
 - (15) -(CH₂)_nSO₂N(R⁶)₂,

- (16) $-(CH_2)_nS(O)_{0-1}R^6$,
- (17) $-(CH_2)_nNR^6C(O)N(R^6)_2$,
- (18) $-(CH_2)_nC(O)N(R^6)_2$,
- (19) $-(CH_2)_nNR^6C(O)R^6$,
- 5 (20) $-(CH_2)_nNR^6CO_2R^6$,
- (21) $-(CH_2)_nNR^6C(O)$ -heteroaryl,
- (22) $-(CH_2)_nC(O)NR^6N(R^6)_2$,
- (23) $-(CH_2)_nC(O)NR^6NR^6C(O)R^6$,
- (24) $O(CH_2)_nC(O)N(R^6)_2$,
- 10 (25) CF_3 ,
- (26) CH_2CF_3 ,
- (27) OCF_3 , and
- (28) OCH_2CF_3 ,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, and wherein any methylene (CH₂) carbon atom in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

20

R⁴ is selected from the group consisting of:

- (1) $-(CH_2)-N(R^5)-NR^5R^6$,
- (2) $-(CH_2)-N(R^5)-(CH_2)_{1-3}-NR^5R^6$,
- (3) $-(CH_2)-N(R^5)-C(=NR^5)-NR^5R^6$,
- 25 (4) $-(CH_2)-N(R^5)-(CH_2)_{1-3}-N(R^5)-(C=NR^5)-NR^5R^6$,
- (5) $-(CH_2)-N(R^5)-(CH_2)_{0-2}-C(R^5)(N(R^5)_2)-(CH_2)_{1-2}-OR^6$,
- (6) $-(CH_2)-N(R^5)-(CH_2)_{0-2}-C(R^5)(N(R^5)_2)(CH_2)_{1-2}-R^6$,
- (7) $-(CH_2)-N(R^5)-(CH_2)_{0-2}-C(R^5)(N(R^5)_2)(CH_2)_{1-2}-S-R^6$,
- (8) $-(CH_2)-N(R^5)-(CH_2)_{0-2}-C(R^5)(N(R^5)_2)(CH_2)_{1-4}-NR^5R^6$,
- 30 (9) $-(CH_2)-N(R^5)-C(O)(CH_2)_{0-2}-C(R^5)(N(R^5)_2)(CH_2)_{1-2}-R^6$,
- (10) $-(CH_2)-N(R^5)-C(O)(CH_2)_{0-2}-C(R^5)(N(R^5)_2)(CH_2)_{1-2}-S-R^6$,
- (11) $-(CH_2)-N(R^5)-C(O)(CH_2)_{0-2}-C(R^5)(N(R^5)_2)(CH_2)_{1-4}-NR^5R^6$, and
- (12) $-(CH_2)-N(R^5)-R^9$,

wherein (CH₂) is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁵ is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl, and
- 5 (3) C(O)C₁₋₆ alkyl,

wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R⁶ is selected from the group consisting of:

- 10 (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) C(O)C₁₋₆ alkyl,
- (4) -(CH₂)_nC₃₋₇ cycloalkyl,
- (5) -(CH₂)_nC₂₋₇ heterocycloalkyl,
- 15 (6) -(CH₂)_n-phenyl,
- (7) -(CH₂)_n-naphthyl,
- (8) -(CH₂)_n-heteroaryl, and
- (9) -(CH₂)_nC₃₋₇ bicycloalkyl,

wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and (CH₂)_n are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy, or wherein two R⁶ groups together with the atom to which they are attached form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

25 each R⁷ and R⁸ is independently selected from the group consisting of:

- (1) hydrogen,
- (2) amidino,
- (3) C₁₋₄ alkyliminoyl,
- (4) C₁₋₁₀ alkyl,
- 30 (5) -(CH₂)_n-C₃₋₇ cycloalkyl,
- (6) -(CH₂)_n-phenyl,
- (7) -(CH₂)_n-naphthyl, and
- (8) -(CH₂)_n-heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with one to three groups independently selected from R³ and oxo;

R⁹ is selected from the group consisting of:

- (1) alanine,
- (2) glycine,
- 5 (3) proline,
- (4) cysteine,
- (5) histidine,
- (6) glutamine,
- (7) aspartic acid,
- 10 (8) isoleucine,
- (9) arginine,
- (10) glutamic acid,
- (11) lysine,
- (12) serine,
- 15 (13) phenylalanine,
- (14) leucine,
- (15) threonine,
- (16) tryptophan,
- (17) methionine,
- 20 (18) valine,
- (19) tyrosine,
- (20) asparagine,
- (21) 2-amino adipic acid,
- (22) beta-alanine,
- 25 (23) 2-aminoheptanedioic acid,
- (24) 2-aminobutyric acid,
- (25) 4-aminobutyric acid,
- (26) 2,4-diaminobutyric acid,
- (27) citrulline,
- 30 (28) cycloserine,
- (29) norvaline,
- (30) norleucine,
- (31) ornithine,
- (32) penicillamine,
- 35 (33) phenylglycine,
- (34) phenylisoserine,

- (35) phenylstatine,
 - (36) pipecolic acid,
 - (37) piperidine carboxylic acid,
 - (38) pyroglutamic acid,
 - (39) sarcosine,
 - (40) statine,
 - (41) allo-threonine,
 - (42) t-leucine,
 - (43) 2-aminoisobutyric acid, and
 - (44) 3-aminoisobutyric acid;

Z is selected from the group consisting of:

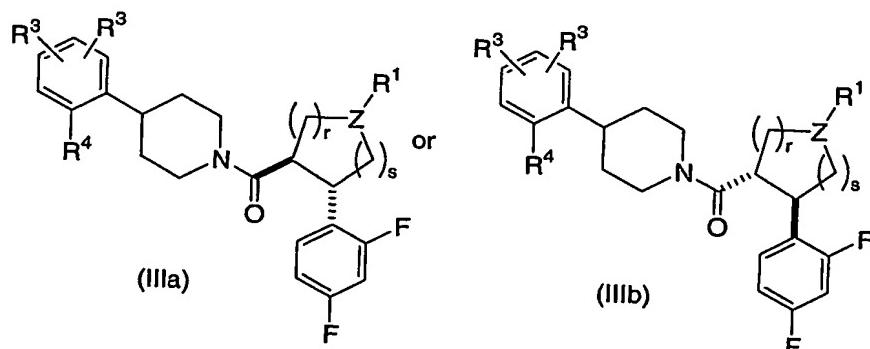
- (1) $C(\mathbb{R}^1)$, and
 (2) \mathbb{N} :

r is 1 or 2.

s is 0, 1 or 2; and

n is 0, 1, 2, 3 or 4

20 13. The compound of Claim 1 of structural formula IIIa or IIIb of the indicated *trans* relative stereochemical configuration:



or a pharmaceutically acceptable salt thereof;
wherein:

25

R¹ is selected from the group consisting of: hydrogen, C₁₋₄ alkyl, and -(CH₂)₀₋₁ phenyl.

each R^3 is independently selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl,
- (3) -(CH₂)_n-phenyl,
- (4) -(CH₂)_n-naphthyl,
- 5 (5) -(CH₂)_n-heteroaryl,
- (6) -(CH₂)_n-heterocycloalkyl,
- (7) -(CH₂)_nC₃₋₇ cycloalkyl,
- (8) halogen,
- 10 (9) OR⁶,
- (10) -(CH₂)_nN(R⁶)₂,
- (11) -(CH₂)_nC≡N,
- (12) -(CH₂)_nCO₂R⁶,
- (13) NO₂,
- 15 (14) -(CH₂)_nNR⁶SO₂R⁶,
- (15) -(CH₂)_nSO₂N(R⁶)₂,
- (16) -(CH₂)_nS(O)₀₋₁R⁶,
- (17) -(CH₂)_nNR⁶C(O)N(R⁶)₂,
- (18) -(CH₂)_nC(O)N(R⁶)₂,
- (19) -(CH₂)_nNR⁶C(O)R⁶,
- 20 (20) -(CH₂)_nNR⁶CO₂R⁶,
- (21) -(CH₂)_nNR⁶C(O)-heteroaryl,
- (22) -(CH₂)_nC(O)NR⁶N(R⁶)₂,
- (23) -(CH₂)_nC(O)NR⁶NR⁶C(O)R⁶,
- (24) O(CH₂)_nC(O)N(R⁶)₂,
- 25 (25) CF₃,
- (26) CH₂CF₃,
- (27) OCF₃, and
- (28) OCH₂CF₃,

wherein phenyl, naphthyl, heteroaryl, cycloalkyl, and heterocycloalkyl are unsubstituted or substituted with one to three substituents independently selected from halogen, hydroxy, oxo, C₁₋₄ alkyl, trifluoromethyl, and C₁₋₄ alkoxy, and wherein any methylene (CH₂) carbon atom in R³ is unsubstituted or substituted with one to two groups independently selected from halogen, hydroxy, and C₁₋₄ alkyl, or wherein two substituents when on the same methylene (CH₂) group are taken together with the carbon atom to which they are attached to form a cyclopropyl group;

35

R⁴ is selected from the group consisting of:

- (1) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-NR}^5\text{R}^6$,
- (2) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-}(\text{CH}_2)_1\text{-}3\text{-NR}^5\text{R}^6$,
- (3) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-C}(=\text{NR}^5)\text{-NR}^5\text{R}^6$,
- (4) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-}(\text{CH}_2)_1\text{-}3\text{-N}(\text{R}^5)\text{-}(\text{C}=\text{NR}^5)\text{-NR}^5\text{R}^6$,
- 5 (5) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-}(\text{CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)\text{-}(\text{CH}_2)_1\text{-}2\text{-OR}^6$,
- (6) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-}(\text{CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_1\text{-}2\text{-R}^6$,
- (7) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-}(\text{CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_1\text{-}2\text{-S-R}^6$,
- (8) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-}(\text{CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_1\text{-}4\text{-NR}^5\text{R}^6$,
- (9) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-C(O)(CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_1\text{-}2\text{-R}^6$,
- 10 (10) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-C(O)(CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_1\text{-}2\text{-S-R}^6$,
- (11) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-C(O)(CH}_2)_0\text{-}2\text{-C}(\text{R}^5)(\text{N}(\text{R}^5)_2)(\text{CH}_2)_1\text{-}4\text{-NR}^5\text{R}^6$, and
- (12) $-(\text{CH}_2)\text{-N}(\text{R}^5)\text{-R}^9$,

wherein (CH_2) is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

15

R^5 is selected from the group consisting of:

- (1) hydrogen,
- (2) C₁₋₆ alkyl, and
- (3) C(O)C₁₋₆ alkyl,

20 wherein alkyl is unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, oxo, and C₁₋₄ alkoxy;

R^6 is selected from the group consisting of:

- (1) hydrogen,
- 25 (2) C₁₋₆ alkyl,
- (3) C(O)C₁₋₆ alkyl,
- (4) $-(\text{CH}_2)_n\text{C}_3\text{-}7$ cycloalkyl,
- (5) $-(\text{CH}_2)_n\text{C}_2\text{-}7$ heterocycloalkyl,
- (6) $-(\text{CH}_2)_n\text{-phenyl}$,
- 30 (7) $-(\text{CH}_2)_n\text{-naphthyl}$,
- (8) $-(\text{CH}_2)_n\text{-heteroaryl}$, and
- (9) $-(\text{CH}_2)_n\text{C}_3\text{-}7$ bicycloalkyl,

35 wherein alkyl, phenyl, heteroaryl, heterocycloalkyl, naphthyl, cycloalkyl, bicycloalkyl and $(\text{CH}_2)_n$ are unsubstituted or substituted with one to three groups independently selected from halogen, C₁₋₄ alkyl, hydroxy, and C₁₋₄ alkoxy, or wherein two R^6 groups together with the atom to which they are attached

form a 4- to 8-membered mono- or bicyclic ring system optionally containing an additional heteroatom selected from O, S, and -NC₁₋₄ alkyl;

each R⁷ and R⁸ is independently selected from the group consisting of:

- 5 (1) hydrogen,
 (2) amidino,
 (3) C₁₋₄ alkyliminoyl,
 (4) C₁₋₁₀ alkyl,
 (5) -(CH₂)_n-C₃₋₇ cycloalkyl,
10 (6) -(CH₂)_n-phenyl,
 (7) -(CH₂)_n-naphthyl, and
 (8) -(CH₂)_n-heteroaryl,

wherein phenyl, naphthyl, and heteroaryl are unsubstituted or substituted with one to three groups independently selected from R³, and wherein alkyl and cycloalkyl are unsubstituted or substituted with 15 one to three groups independently selected from R³ and oxo;

R⁹ is selected from the group consisting of:

- 20 (1) alanine,
 (2) glycine,
 (3) proline,
 (4) cysteine,
 (5) histidine,
 (6) glutamine,
 (7) aspartic acid,
25 (8) isoleucine,
 (9) arginine,
 (10) glutamic acid,
 (11) lysine,
 (12) serine,
30 (13) phenylalanine,
 (14) leucine,
 (15) threonine,
 (16) tryptophan,
 (17) methionine,
35 (18) valine,
 (19) tyrosine,

- (20) asparagine,
- (21) 2-amino adipic acid,
- (22) beta-alanine,
- (23) 2-aminoheptanedioic acid,
- 5 (24) 2-aminobutyric acid,
- (25) 4-aminobutyric acid,
- (26) 2,4-diaminobutyric acid,
- (27) citrulline,
- (28) cycloserine,
- 10 (29) norvaline,
- (30) norleucine,
- (31) ornithine,
- (32) penicillamine,
- (33) phenylglycine,
- 15 (34) phenylisoserine,
- (35) phenylstatine,
- (36) pipecolic acid,
- (37) piperidine carboxylic acid,
- (38) pyroglutamic acid,
- 20 (39) sarcosine,
- (40) statine,
- (41) allo-threonine,
- (42) t-leucine,
- (43) 2-aminoisobutyric acid, and
- 25 (44) 3-aminoisobutyric acid;

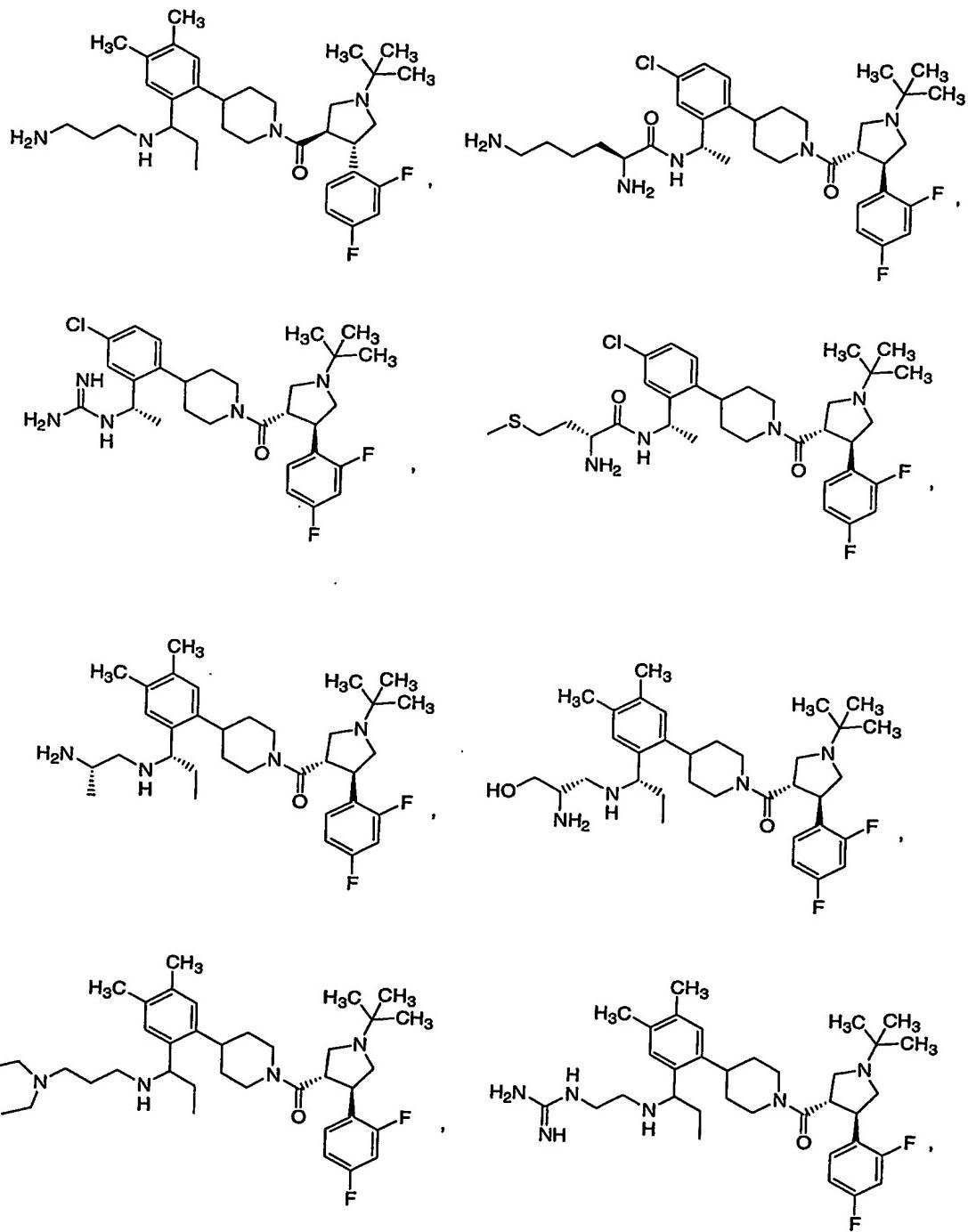
Z is selected from the group consisting of:

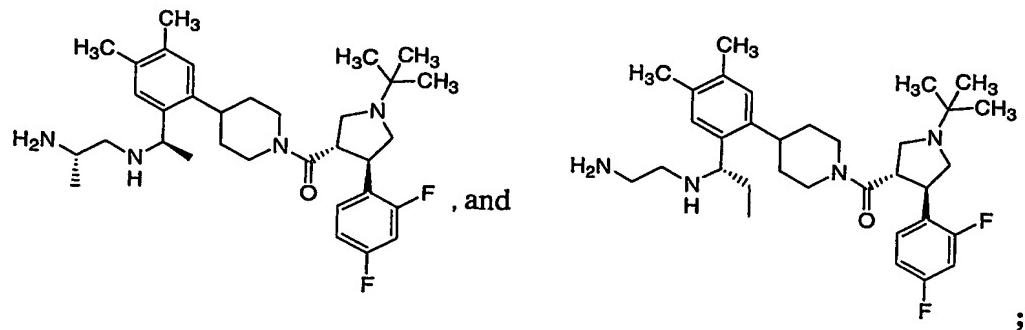
- (1) C(R¹), and
- (2) N;

30

- r is 1 or 2;
- s is 0, 1, or 2; and
- n is 0, 1, 2, 3, or 4.

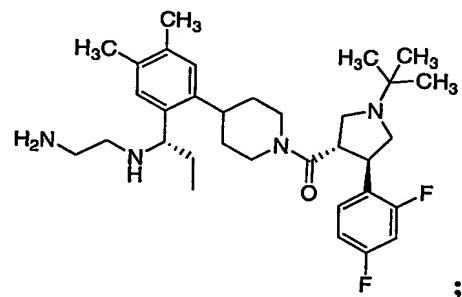
35 14. The compound of Claim 13 selected from the group consisting of:





or a pharmaceutically acceptable salt thereof.

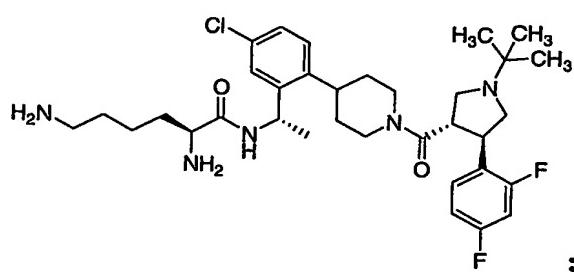
15. The compound of Claim 14 which is:



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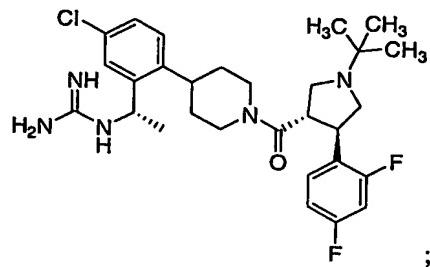
or a pharmaceutically acceptable salt thereof.

16. The compound of Claim 14 which is:



10 or a pharmaceutically acceptable salt thereof.

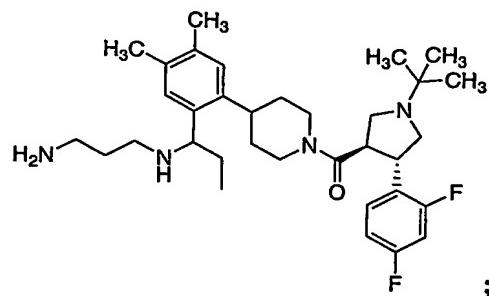
17. The compound of Claim 14 which is:



or a pharmaceutically acceptable salt thereof.

18. The compound of Claim 14 which is:

5



or a pharmaceutically acceptable salt thereof.

19. A method for the treatment or prevention of disorders, diseases or conditions responsive

10 to the activation of the melanocortin-4 receptor in a mammal in need thereof which comprises
administering to the mammal a therapeutically or prophylactically effective amount of a compound
according to Claim 1.

20. A method for the treatment or prevention of obesity in a mammal in need thereof which

15 comprises administering to the mammal a therapeutically or prophylactically effective amount of a
compound according to Claim 1.

21. A method for the treatment or prevention of diabetes mellitus in a mammal in need
thereof comprising administering to the mammal a therapeutically or prophylactically effective amount

20 of a compound according to Claim 1.

22. A method for the treatment or prevention of male or female sexual dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

5 23. A method for the treatment or prevention of erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

10 24. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

15 25. The pharmaceutical composition of Claim 24 further comprising a second active ingredient selected from the group consisting of: an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, a HMG-CoA reductase inhibitor, a serotonergic agent, a β 3-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB₁ receptor antagonist or inverse agonist, a melanin-concentrating hormone receptor antagonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, and a dipeptidyl peptidase IV inhibitor.

20 26. The pharmaceutical composition of Claim 24 further comprising a second active ingredient selected from the group consisting of: a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α 2-adrenergic receptor antagonist, and a dopaminergic agent.

25 27. A method of treating erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of the composition of Claim 24.

30 28. A method of treating erectile dysfunction in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with a type V cyclic-GMP-selective phosphodiesterase inhibitor, an α 2-adrenergic receptor antagonist, or a dopaminergic agent.

29. A method of treating diabetes in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of the composition of Claim 24.

35 30. A method of treating obesity in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of the composition of Claim 24.

31. A method of treating diabetes or obesity in a mammal in need thereof comprising administering to the mammal a therapeutically effective amount of a compound of Claim 1 in combination with an insulin sensitizer, an insulin mimetic, a sulfonylurea, an α -glucosidase inhibitor, a HMG-CoA reductase inhibitor, a serotonergic agent, a β 3-adrenoreceptor agonist, a neuropeptide Y1 antagonist, a neuropeptide Y5 antagonist, a pancreatic lipase inhibitor, a cannabinoid CB₁ receptor antagonist or inverse agonist, a melanin-concentrating hormone receptor antagonist, a bombesin receptor subtype 3 agonist, a ghrelin receptor antagonist, or a dipeptidyl peptidase IV inhibitor.

10 32. A method of treating an obesity-related disorder selected from the group consisting of: overeating, binge eating, and bulimia, hypertension, diabetes, elevated plasma insulin concentrations, insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, metabolic syndrome, insulin resistance syndrome, sexual and reproductive dysfunction, infertility, hypogonadism, hirsutism, obesity-related gastro-esophageal reflux, Pickwickian syndrome, cardiovascular disorders, inflammation, systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer, cardiac hypertrophy and left ventricular hypertrophy, in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

25 33. A method of preventing an obesity-related disorder selected from the group consisting of: overeating, binge eating, and bulimia, hypertension, diabetes, elevated plasma insulin concentrations, insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, metabolic syndrome, insulin resistance syndrome, sexual and reproductive dysfunction, infertility, hypogonadism, hirsutism, obesity-related gastro-esophageal reflux, Pickwickian syndrome, cardiovascular disorders, inflammation, systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer, cardiac hypertrophy and left ventricular hypertrophy, in a mammal in need thereof which comprises administering to the mammal a therapeutically or prophylactically effective amount of a compound according to Claim 1.

34. The compound of Claim 14 wherein the pharmaceutically acceptable salt is the hydrochloride salt.

5 35. The compound of Claim 14 wherein the pharmaceutically acceptable salt is the trifluoroacetic acid salt.

10 36. The use of a compound according to Claim 1 for the manufacture of a medicament useful for the treatment of a disease mediated by the melanocortin-4 receptor in a human subject in need thereof.

15 37. The use according to Claim 36 wherein the disease mediated by the melanocortin-4 receptor is selected from the group consisting of: obesity, diabetes, male sexual dysfunction and female sexual dysfunction.

38. The use according to Claim 37, wherein the male sexual dysfunction is male erectile dysfunction.

20 39. The use of a compound according to Claim 1 for the manufacture of a medicament useful for the prevention of a disease mediated by the melanocortin-4 receptor in a human subject at risk thereof.

25 40. The use according to Claim 39 wherein the disease mediated by the melanocortin-4 receptor is selected from the group consisting of: obesity, diabetes, male sexual dysfunction and female sexual dysfunction.

41. The use according to Claim 40, wherein the male sexual dysfunction is male erectile dysfunction.

30 42. The use of a compound according to Claim 1 for the manufacture of a medicament useful for the treatment or prevention of an obesity-related disorder selected from the group consisting of: overeating, binge eating, and bulimia, hypertension, diabetes, elevated plasma insulin concentrations, insulin resistance, dyslipidemias, hyperlipidemia, endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms, arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovary disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome,

GH-deficient subjects, normal variant short stature, Turner's syndrome, metabolic syndrome, insulin resistance syndrome, sexual and reproductive dysfunction, infertility, hypogonadism, hirsutism, obesity-related gastro-esophageal reflux, Pickwickian syndrome, cardiovascular disorders, inflammation, systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer, cardiac hypertrophy and left ventricular hypertrophy.

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